DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

MEMORANDUM Food and Drug Administration

DATE: June 18, 1998

FROM: Robert W. Anderson, Ph.D., CGTB

TO: License File Number 1252

SUBJECT: MedImmune, Inc. Summary Basis of Approval

BLA: 97-1359

Manufacturer: MedImmune, Inc.
35 West Watkins Mill Road
Gaithersburg, MD 20878

Established Name: Palivizumab

Trade Name: Synagis

Background:

Synagis™, palivizumab, is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to the A epitope of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the VH genes Cor and Cess. The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the VL gene K104 with Jκ-4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process which involved the grafting of the murine complementary determining regions into the human antibody frameworks. Synagis™ is composed of two heavy chains and two light chains, has a molecular weight of approximately 148,000 Daltons.

Synagis exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis. Synagis serum concentrations of ≥ 40 μg/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Indications and Usage

Synagis (Palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with broncho-pulmonary dysplasia (BPD) and infants with a history of prematurity (≤35 weeks gestational age).

Dosage Form, Route of Administration, and Recommended Dosage

Synagis is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Upon reconstitution Synagis contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per vial. This product contains no preservatives.

The recommended dose of Synagis is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose should be administered prior to the commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in a community.

Synagis should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = [patient weight (kg) X 15 mg/kg ÷ 100 mg/ml of Synagis]. Injection volumes over 1 ml should be given as a divided dose.

Basis for Approval

The basis of approval for Synagis for prophylaxis of serious lower respiratory tract disease, caused by respiratory syncytial virus, in pediatric patients at high risk of RSV disease is contained in the following appended documentation:

1. Committee Memo/Kozlowski: Recommend Approval
2. Review Memo/Kozlowski: CMC Section of BLA (Product)
3. Review Memo/Brown: CMC Section of BLA (Facility)
4. Review Memo/Serabian: Pharmacology/Toxicology Section of BLA
5. Review Memo/Rieves: Clinical Safety and Efficacy Section of BLA
6. Review Memo/Neeman: Statistical Analysis of Safety and Efficacy Data
7. Review Memo/Andrich: Bioresearch Monitoring Inspection Summary